DATA SUPPLEMENT
Intrinsic frequencies of carotid pressure waveforms predict heart failure events: the Framingham Heart Study

Leroy L. Cooper, PhD, MPH,[1] Jian Rong, PhD,[2] Niema M. Pahlevan, PhD,[3,4] Derek G. Rinderknecht, PhD,[5] Emelia J. Benjamin, MD, ScM,[2,6,7,8,9] Naomi M. Hamburg, MD, MS,[7,8] Ramachandran S. Vasan, MD,[2,6,7,8,9] Martin G. Larson, ScD,[2,10] Morteza Gharib, PhD,[5,11] and Gary F. Mitchell, MD[12]

[1]Biology Department, Vassar College, Poughkeepsie, NY; [2]Boston University and NHLBI's Framingham Heart Study, Framingham, MA; [3]Department of Aerospace and Mechanical Engineering, University of Southern California, Los Angeles, CA; [4]Department of Medicine, Division of Cardiovascular Medicine, Keck School of Medicine, University of Southern California; [5]Graduate Aerospace Laboratories, Division of Engineering and Applied Sciences, California Institute of Technology, Pasadena, CA; [6]Cardiology and Preventive Medicine Sections, Department of Medicine, Boston University School of Medicine, Boston, MA; [7]Evans Department of Medicine, [8]Whitaker Cardiovascular Institute, Boston University School of Medicine, Boston, MA; [9]Department of Epidemiology, Boston University School of Public Health; and [10]Department of Biostatistics, Boston University School of Public Health, Boston, MA; [11]Department of Medical Engineering, California Institute of Technology, Pasadena, CA, USA; and [12]Cardiovascular Engineering, Inc., Norwood, MA

Supplemental Content:

This supplementary material has been provided by the authors to give the readers additional information about their work.

Supplemental Methods: Intrinsic frequency (IF) method based on the Sparse Time-Frequency Representation (STFR)

In Sparse Time-Frequency Representation (STFR) method, a signal s(t) is decomposed into a finite sum of Intrinsic Mode Functions ($\mathrm{IMF} = \mathrm{R}(\mathrm{t})\cos\theta\,(\mathrm{t})$):[13]

$$\mathrm{s}(\mathrm{t}) = \sum_{\mathrm{i}=1}^{\mathrm{M}} \mathrm{R}_{\mathrm{i}}(\mathrm{t})\cos\theta_{\mathrm{i}}\,(\mathrm{t}) \qquad \text{(S.1)}$$

Here, $\mathrm{R}_{\mathrm{i}}(\mathrm{t})$is called the envelope and $\theta_{\mathrm{i}}(\mathrm{t})$is the phase. The time derivative of θ_{i} is the instantaneous frequency ($\mathrm{d}\theta_{\mathrm{i}}/\mathrm{dt}$). STFR finds the sparsest representation of IMFs. In other words, it minimizes M in equation S1 where M is the total number of IMFs. Details of the STFR mathematics and computation were in the previous publications.[13, 23] Each IMF models the dynamical system as an object rotating around an origin with time dependent radius (envelope) and time dependent angular velocity (instantaneous frequency). The intrinsic frequency (IF) method assumes that the envelope and instantaneous frequency are piecewise constant in time with the step at the decoupling time (i.e. the time of the dicrotic notch). Our proposed IF method for the LV-arterial system only considers the first IMF, which carries the maximum signal energy. The IF representation of a single pressure waveform for the first IMF is:

$$\tilde{\mathrm{p}}(\mathrm{t}) = \chi(0,\mathrm{T}_0)[(\mathrm{a}_1\cos(\omega_1\mathrm{t}) + \mathrm{b}_1\sin(\omega_1\mathrm{t})] + \chi(\mathrm{T}_0,\mathrm{T})[(\mathrm{a}_2\cos(\omega_2\mathrm{t}) + \mathrm{b}_2\sin(\omega_2\mathrm{t})] + \mathrm{c} \qquad \text{(S.2)}$$

Here, $\chi(0,\mathrm{T}_0) = 1$ if $0 \le \mathrm{t} \le \mathrm{T}_0$ and $\chi(0,\mathrm{T}_0) = 0$ otherwise. Similarly, $\chi(\mathrm{T}_0,\mathrm{T}) = 1$ if $\mathrm{T}_0 \le \mathrm{t} \le \mathrm{T}$ and $\chi(\mathrm{T}_0,\mathrm{T}) = 0$ otherwise. a_1, a_2, b_1, b_2, c, ω_1, and ω_2 can be solved using an L-2 minimization procedure as described in the manuscript methods section. Note that the envelope $\mathrm{R}_1(\mathrm{t})$ is a piecewise constant function in time with the step at T_0 and can be computed from a_1, a_2, b_1, and b_2 as $\mathrm{R}_{\mathrm{s}} = \sqrt{\mathrm{a}_1^2 + \mathrm{b}_1^2}$ and $\mathrm{R}_{\mathrm{d}} = \sqrt{\mathrm{a}_2^2 + \mathrm{b}_2^2}$ where R_s and R_d are the envelope of intrinsic frequencies associated with ω_1 (before T_0) and ω_2 (after T_0), respectively.

Table S1. Comparison of clinical characteristics between included and excluded participants.

Variable	Included	Excluded*
Clinical measures		
Age, y	52±13	37±18
Women, No. (%)	2577 (55)	626 (51)
Body mass index, kg/m^2	26.9±5.0	25.9±4.8
Systolic blood pressure, mm Hg	122±18	117±16
Diastolic blood pressure, mm Hg	75±10	72±10
Pulse pressure, mm Hg	53±13	56±12
Mean arterial pressure, mm Hg	91±12	86±11
End-systolic pressure, mm Hg	99±13	92±13
Heart rate, beats per minute	63±10	62±10
Total cholesterol, mg/dL	196±35	178±34
High-density lipoprotein cholesterol, mg/dL	55±17	53±15
Systolic ejection period, ms	313±25	310±24
Carotid-femoral pulse wave velocity, m/s	8.7±3.3	7.5±3.7
Hypertension treatment, No. (%)	994 (21)	165 (14)
Diabetes mellitus, No. (%)	229 (5)	69 (6)
Smoker, No. (%)	657 (14)	187 (15)
Generation 3 Exam 1, No. (%)	2567 (55)	1010 (83)

All values are mean±standard deviation except as noted. *N varies for excluded participants based on availability of data. SI conversions factor: to convert total cholesterol and high-density lipoprotein cholesterol to mmol/L, multiply by 0.0259.

Table S2. Matrix of Pearson partial correlation coefficients for novel intrinsic frequencies and demographic data (N=4700).

Variables	Age*	Sex†	TC	HDL	BMI	HTN	DM	Smoker
ω_1	0.05 0.001	-0.13 <0.001	0.10 <0.001	-0.10 <0.001	0.09 <0.001	0.05 <0.001	0.10 <0.001	0.12 <0.001
ω_2	-0.25 <0.001	-0.16 <0.001	-0.12 <0.001	0.02 0.14	0.01 0.53	-0.02 0.17	-0.02 0.11	-0.17 <0.001
$\Delta\omega$	0.22 <0.001	0.09 <0.001	0.12 <0.001	-0.05 0.002	0.02 0.22	0.03 0.30	0.05 0.002	0.17 <0.001

TC, total cholesterol. HDL, high-density lipoprotein cholesterol. BMI, body mass index. HTN, presence of hypertension treatment. DM, prevalent of diabetes mellitus. Top value is partial *r*; bottom value is *P* in each cell. All correlations are adjusted for age, sex, and cohort except for age (*adjusted for sex and cohort) and sex (†adjusted for age and cohort). Partial *r* values for binary-continuous pairs of variables are equal to point biserial correlations.

Table S3. Individual intrinsic frequency measures as predictors of incident CVD event with further adjustment with systolic ejection period (N=4700).

IF Measure	Composite CVD Events (N=371) HR (LCL, UCL)	*P*	MI Events (N=147) HR (LCL, UCL)	*P*	HF Events (N=152) HR (LCL, UCL)	*P*	Stroke Events (N=116) HR (LCL, UCL)	*P*
ω_1	1.17 (1.04, 1.31)	0.012	1.08 (0.89, 1.31)	0.46	1.30 (1.10, 1.53)	0.002	1.02 (0.82, 1.27)	0.87
ω_2	0.88 (0.77, 1.00)	0.046	0.90 (0.74, 1.10)	0.30	0.81 (0.66, 0.99)	0.04	1.03 (0.82, 1.28)	0.82
$\Delta\omega$	1.15 (1.02, 1.31)	0.025	1.11 (0.91, 1.35)	0.31	1.26 (1.04, 1.53)	0.02	0.99 (0.79, 1.23)	0.89

IF, intrinsic frequency. MI, myocardial infarction. HF, heart failure. Hazard ratios (HRs) expressed per 1 standard deviation higher value. LCL, UCL, lower and upper limits of the 95% confidence intervals. Models add intrinsic frequency measures to the covariates individually, one at a time. All models adjusted for age, sex, cohort, body mass index, systolic blood pressure, diastolic blood pressure, heart rate, total cholesterol, high-density lipoprotein cholesterol, smoking (current vs. nonsmoker), diabetes mellitus, hypertension treatment, and systolic ejection period.

Figure S1: Reconstruction of IF with various values of ω_1 and ω_2. IF reconstruction red overlaid on top of the original raw carotid pressure waveforms (black) in arbitrary units (AU) from Framingham participants. The portions of the reconstructed IF represented by ω_1 and ω_2 are before and after notch, respectively.

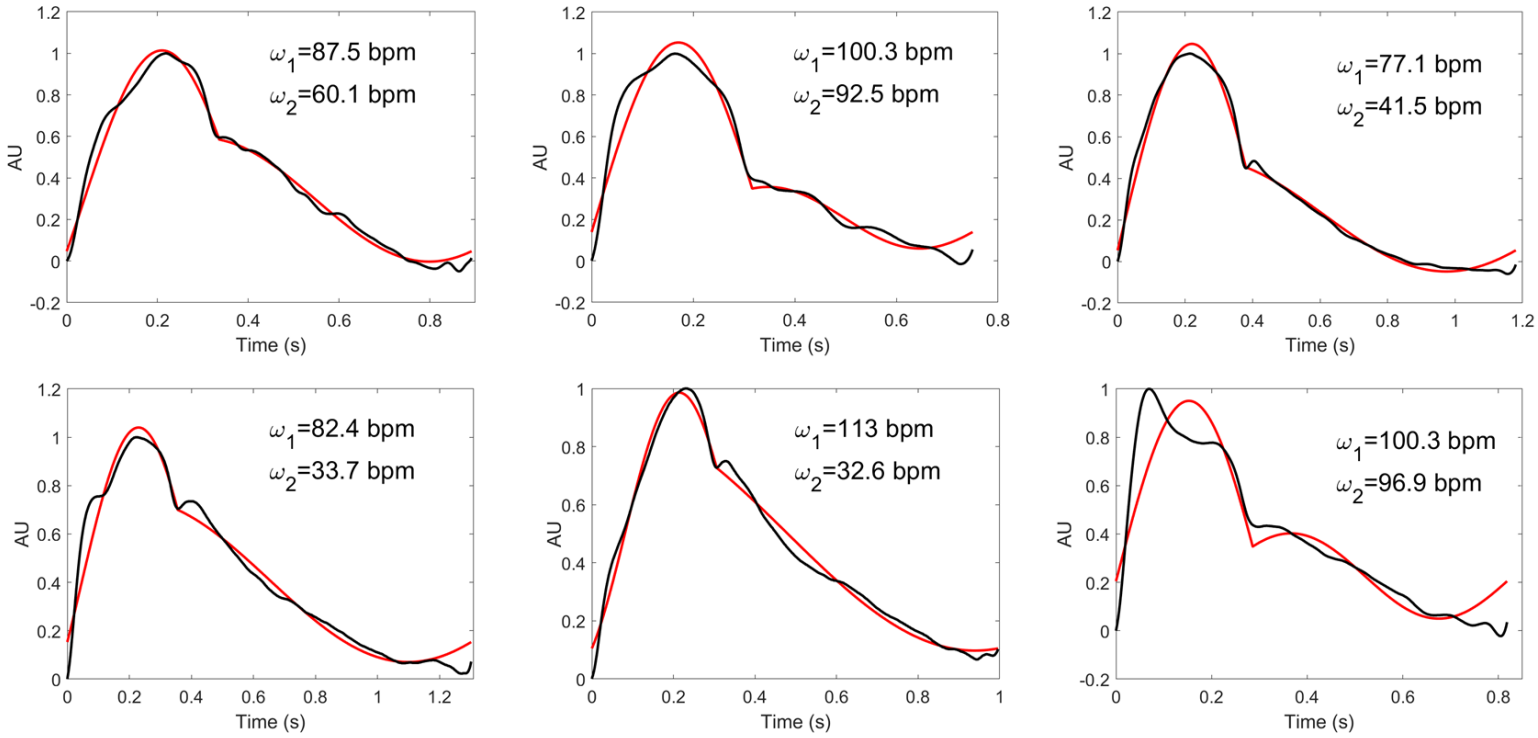

Figure S2. Partial correlation plots for IF variables and hemodynamic measures. Residuals for IF variables regressed on sex and age are plotted against residuals for hemodynamic variables regressed on sex and age. HR, heart rate. SBP, systolic blood pressure. DBP, diastolic blood pressure. ESP, end-systolic pressure. PP, pulse pressure. MAP, mean arterial pressure. CFPWV, carotid-femoral pulse wave velocity.

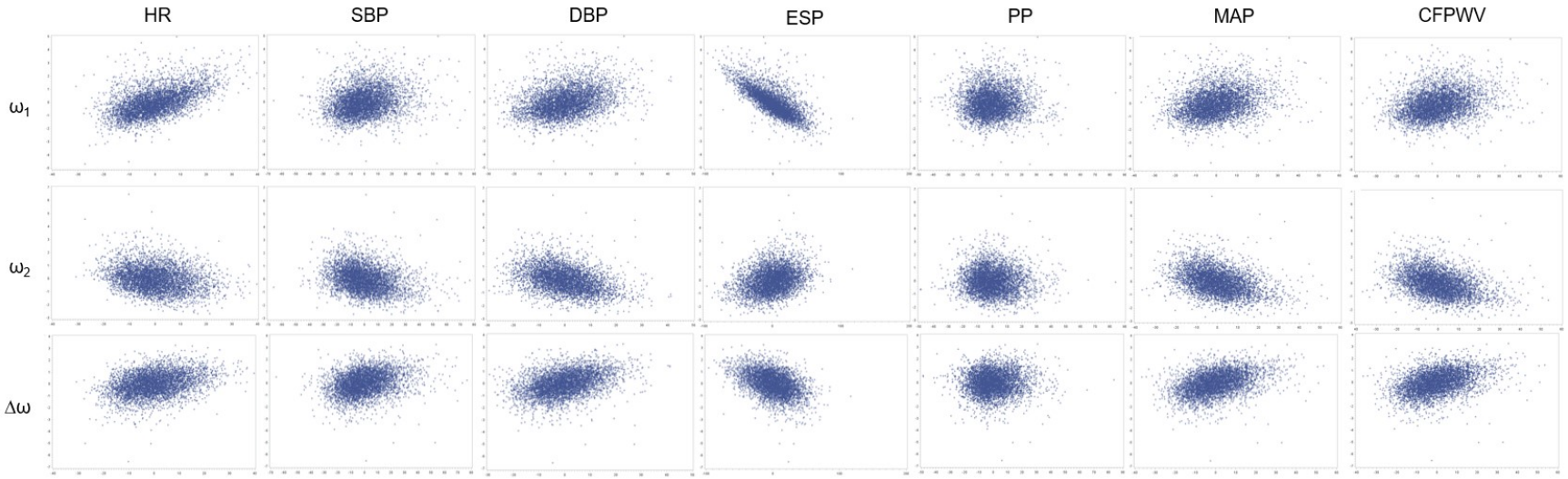

Figure S3: Kaplan-Meier curves of cumulative probability of heart failure when participants were grouped according to quartiles of each intrinsic frequency measure. Incident heart failure (HF) per person for quartile groups of intrinsic frequency measures (A-C). A. ω_1: Group I (<91.8 bpm, 30/1175 [2.6%]); Group II (91.8 to <94.2 bpm, 26/1175 [2.2%]), Group III (94.2 to <96.9 bpm, 36/1175 [3.1%]); and Group IV (≥96.9 bpm, 60/1175 [5.1%]). B. ω_2: Group I (<62.9 bpm, 74/1175 [6.3%]); Group II (62.9 to <71.2 bpm, 37/1175 [3.1%]), Group III (71.2 to <80.1 bpm, 30/1175 [2.6%]); and Group IV (≥80.1 bpm, 11/1175 [0.9%]). C. Δω: Group I (<12.4 bpm, 12/1175 [1.0%]); Group II (12.4 to <22.9 bpm, 29/1175 [2.5%]), Group III (22.9 to <33.2 bpm, 41/1175 [3.5%]); and Group IV (≥33.2 bpm, 70/1175 [6.0%]).